IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:
Zhang *et al.*

Serial No.: 09/203,078

Filed: December 1, 1999

For: METHOD FOR THE PRODUCTION AND PURIFICATION OF ADENOVIRAL VECTORS

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§ Group Art Unit: 1632
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§ Examiner: Foley, Shannon A.
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December 19, 2005 — Date

Gina N. Shishima

APPELLANTS' REPLY TO EXAMINER'S ANSWER

OVERVIEW OF ARGUMENT

The claims that are currently rejected as anticipated by Huyghe *et al.* ("Huyghe"), claims 1, 3, 8, 9, 13-25, 31, 38, 47, 49 and 51-62, include a step concerned with infection of a producer cell culture with adenovirus, wherein producer cells in the culture are *between mid-log and stationary phase of growth* at the time of infection. Yet, Huyghe is silent as to whether its producer cells are between mid-log and stationary phase – all we know is that the Huyghe cells had been cultured for 48-60 hours and were 50-60% confluent at the time of infection. Moreover, Huyghe is not even concerned with infection timing issues. Thus, to maintain the anticipation rejection it is the Examiner's burden to present substantial evidence that supports a conclusion that the fact that the Huyghe cells were between mid-log and stationary phase was "necessarily present," *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991), and that such a reasoning "necessarily flows" from Huyghe. *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). The Examiner's Answer in no way satisfies this burden.

It is evident that there is simply insufficient information in Huyghe to determine the phase of the Huyghe cells with any degree of certainty: absent information regarding seeding density, lag phase and doubling times, and without this knowledge, there is no way to conclude that Huyghe infected the cells between mid-log and stationary phase. See Exh. 2, Gallagher Dec, para. 6. None of this information is contained in Huyghe. Nevertheless, Mr. Gallagher does provide information that demonstrates that it more likely than not that the Huyghe cells *were not* between mid-log and stationary phase, most notably 1) calculations carried out by Mr. Gallagher, in which he made assumptions regarding seeding density, lag phase and doubling time, and 2)

the Mediatech reference, which teaches that to obtain log phase cells, one must "check for cultures that appear at least 70% confluent." Exh. 3, p. 1, col. 2, lns 1-6. The Mediatech reference is particularly relevant in that it states that to assure that the cells are in "log" phase one must use at least 70% confluent cultures – and THIS is merely to ensure "log phase" cells, as opposed to the "greater than mid-log" phase cells of the present invention (which would likely require cultures somewhat higher than 70% confluent). The expert declarant, Mr. Gallagher, actually states that Mediatech stands for the proposition that in order to ensure that the culture is in log phase at all (*i.e.*, in early log phase), one has to collect 70% confluent cells.

Thus, the Examiner is relegated to arguing, in essence, that the Kuchler reference (a textbook referred to by Mr. Gallagher for the general proposition that lag times for cells are between 24 and 48 hours), stands for the proposition that the 293 cells of Huyghe, incubated for 60 hours, must have been at mid-log phase. There is simply no basis for such a conclusion! The Kuchler figure relied upon by the Examiner, Figure 3-1 on page 91, is only a very general pictograph that Kuchler uses simply to demonstrate the general shape of a growth curve. This is explained in the text on page 90. Importantly, there is simply no cognizable basis for correlating Figure 3-1 with Huyghe:

- Figure 3-1 involves mouse L-M fibroblast cells, which are vastly different from the human 293 cells of Huyghe

The Examiner attempts to counter this by arguing that since Mr. Gallagher referred to Kuchler in his declaration, then Appellants have somehow admitted the relevance of everything in Kuchler to Appellants' invention. In response, Mr. Gallagher, for the purposes of attempting to calculate the cell phase of the Huyghe 293 cells, refers only to the very general section of

Kuchler, a cell culture textbook, for a general understanding of "lag time." Mr. Gallagher never refers to the L-M mouse fibroblast date of Figure 3-1, and never equates the growth characteristics of mouse L-M fibroblasts to those of human 293 cells.

- The Examiner has carried out an ad-hoc "measurement" which he says shows that the 60 hour time point correlates to mid-log phase.

We would respond by noting that Figure 3-1 is simply a cartoon of sorts and clearly not intended to convey any specific scientifically cognizable information even about L-M growth parameters, much less those of the unrelated human 293 cells. Moreover, we submit that any "evidence" introduced by the Examiner, absent a declaration or affidavit, is simply not evidence. Even if it was, Appellants contend it shows just the opposite: that the 60 hour time period exhibits cells either "at" or "below" mid-log.

- The Doubling Time of 293 Cells v. L-M Cells/Lag Time/Seeding Density of Figure 3-1

The Examiner's reasoning is that Kuchler evidences that cells such as 293 cells, if incubated for 60 hours, will necessarily be past mid-log phase. This totally non-scientific, non-sequeter argument relies on an underlying assumption that in both Huyghe and Kuchler the same number of cells were seeded, and that the 293 cells in Huyghe and the L-M mouse fibroblasts of Kuchler have precisely the same lag time, and that both cell types have the same doubling time. The Examiner makes no attempt to fill in these blanks, instead attempting to rely entirely on what he posits is some kind of admission by Mr. Gallagher that all of these parameters are the same. This simply is not sufficient to satisfy the reasonable certainly requirement of the caselaw. Moreover, a careful study of the Kuchler's Figure 3-1 shows that in fact the doubling time of the L-M cells there, about 16-20 hours, as compared to, for example, an exemplary 30 to 36 hour

doubling time for 293 cells. If the 293 cells of Huyghe had a longer doubling time than the 16-20 hour doubling of the Kuchler L-M mouse fibroblasts, then the Examiner's logic would lead one to conclude that the Huyghe culture clearly did not reach mid-log.

In short, there is simply no basis for concluding that the Examiner has met his burden of establishing a *prima facie* case of anticipation over Huyghe that based on substantial evidence. Moreover, we would note claims 1, 3, 8, 9, 13-25, 31, 38, 47, 49 and 51-62 are rejected only on the basis of the anticipation rejection. Thus, if the Board finds this rejection insufficient, these claims should be in condition for allowance.

Moreover, if no *prima facie* case has been made with respect to the anticipation over Huyghe, then we submit that the remaining obviousness rejections, all of which are based on Huyghe, can not stand either. Nevertheless, we have presented additional evidence and argument with respect to the secondary references and obviousness rejections as well.

1. The Examiner's Burden of Showing Anticipation has Not Been Met

The Examiner has not made a *prima facie* case of anticipation because he has not shown that Huyghe in light of Kuchler, in accordance with the requirements of *Verdegaal Bros. v. Union Oil Co. of California*, either expressly or inherently described each limitation of the claimed invention. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987).

The Examiner's rejection of the aforementioned claims is apparently based on inherent anticipation as no evidence has been presented to show that Huyghe expressly discloses infection of producer cells with adenovirus between mid-log and stationary phase of growth. However,

the Examiner has not met the burden of establishing inherent anticipation because the Examiner has neither shown that the characteristics of the present invention are necessarily present in the prior art, nor provided a basis to reasonably support such a determination. "Anticipation by inherency requires that 1) the missing descriptive matter be 'necessarily present' in the prior art reference and that 2) it would be so recognized by persons of ordinary skill in the art." *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991). "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990).

2. The Examiner Has Not Established That the Missing Descriptive Matter is Necessarily Present in the Prior Art

The Examiner has attempted, yet failed, to establish inherent anticipation of the present invention by Huyghe in light of Kuchler by showing that the allegedly inherent characteristic, infection of producer cells between mid-log and stationary phase of growth, "necessarily" flows from the teachings of the prior art. More specifically, the Examiner contends that the cells of Huyghe are at mid-log phase at the time of infection based on the following: "1) lag time of 293 cells ranges between 24-48 hours, 2) the cells of Huyghe have a confluency of 50-60% upon infection, 3) the cells of Huyghe attach to the surface of the plate for 48-60 hours before infection, which is beyond lag phase time, and 4) the chart provided by Kuchler indicates that the growth curve of cells after 60 hours of incubation is the mid-point of the growth curve, *i.e.*, mid-phase." (Office Action, June 3, 2004, page 7, paragraph 2) This same rejection is maintained for reasons of record in the Office Action Dated November 17, 2004 (page 6, paragraph 2).

However, the Examiner's reliance on Kuchler is inappropriate. Moreover, Huyghe is silent as to crucial information regarding log-phase.

3. The Examiner Has Not Provided Objective Evidence to Reasonably Support a Determination of Inherency

The Examiner must provide objective evidence (factual or technical) to reasonably support a determination of inherency. Because the Examiner has not done so, there can be no reasonable support for a determination that that Huyghe infected 293 cells at mid-log based on the chart provided by Kuchler. Based on a previous misunderstanding by the Examiner, in which phases of the cell growth were confused with phases of the cell cycle (G1, S, G2 and M), the Declaration of Shawn Gallagher under 37 C.F.R. § 1.132 and references such as Kuchler were provided in response. Kuchler was provided to illustrate the concept that lag phase, which proceeds log phase, varies between 24 and 48 hours. The Kuchler reference also provides a chart as an example of a growth curve. However, any reliance on this growth curve as being applicable to the cells of Huyghe is misplaced. Simply put, Kuchler shows the growth curve of *mouse* L-M fibroblasts grown in *suspension*, while Huyghe discloses the culture of attached human 293 cells. If the Examiner must provide objective evidence (factual or technical) to reasonably support a determination of inherency, then the Examiner must provide objective evidence to support applying the growth curve of L-M fibroblasts in suspension to the cells taught by Huyghe. Instead, of providing any such reasoning, the Examiner has argued that the Appellants have drawn a nexus. Because the Appellants have indicated that the lag phase period of 24 to 48 hours, as discussed by Kuchler, applies to the cells of Huyghe, the Examiner contends that another nexus may be drawn. More specifically, the Examiner states that "[t]he Office has applied the same nexus between the cells of Kuchler and Huyghe, established by the Appellant, with respect to the log phase of cell growth." Examiner's Answer, page 14. This

conclusion is misplaced. Kuchler discloses that the lag phase is the period in which "the cells do not divide but are in the process of adapting to the new medium." Kuchler, page 90. Separately, the log phase of cell culture is the phase "in which cell number is increasing at a constant rate." *Id.* Kuchler does not appear to suggest that a similarity between cells in the length of lag-phase must 'necessarily' equate to the same constant rate of cell increase (doubling time) during log-phase. Likewise, the Appellants have made no such connection. Moreover, Kuchler appears to indicate that doubling time is variable, stating "[t]he population doubling time for cultured cells ranges from 12 to 48 hours." *Id.*, pages 90-91. Thus, the Examiner has not shown where Kuchler teaches that the growth curve data of L-M fibroblasts in a suspension culture should be used as the standard to determine the particular phase of growth for *any* mammalian cell in *any* culture system. Accordingly, no factual or technical evidence has been provided by the Examiner to reasonably support a determination of inherency.

4. The Chart in Kuchler is Insufficient to Establish Inherent Anticipation

The Appellants also argue in the alternative, that even if Kuchler were relevant to what Huyghe teaches, the Kuchler chart is insufficient to establish inherent anticipation. The Appellants contend that the Examiner erred equating the growth properties of suspension cultured of the Kuchler chart with the attached culture human cells of Huyghe. In viewing the Kuchler chart, it appears as though the L-M cells (mouse fibroblasts) had a 16-20 hour doubling rate, an assumption not apparently challenged by the Examiner. In contrast, the human 293 cells have a doubling rate of 30-36 hours. Thus, even if, as the Examiner emphatically argues, 60 hours is the mid log point on the Kuchler chart, it applies to more rapidly dividing cells. If, on the other hand, the Examiner had substituted the 16-20 hour doubling rate of the L-M cells for a slower 30 hour doubling rate of 293 cells, it appears that the growth curve at 60 hours would be

noticeably below mid-log. Moreover, the Appellants contend that the growth curve shows even the L-M fibroblasts to be slightly before mid-log at 60 hours. Accordingly, the Kuchler chart simply does not provide evidence that the cells of Huyghe were infected after mid-log phase of growth.

5. Huyghe is insufficient to establish Inherent Anticipation

The Examiner has made several statements on the record indicating a failure to establish a prima facie case of anticipation of Huyghe. Briefly, even though the burden had not been shifted, the Appellants previously submitted, along with the Declaration of Shawn Gallagher, a reference from Mediatech. Mr. Gallagher characterized this reference as indicating that in order to ensure cultures are in log phase, they must be at lease 70% confluent, thereby concluding that it is unlikely that the 50-60% confluent cultures of Huyghe could be in log phase at all. The Examiner challenged the sufficiency of this reference.

- The Examiner argues on the record that "a definite identification of which log phase a cell culture is in based on a percentage of confluency cannot be determined."

- The Examiner admits that the Mediatech reference "clearly indicates a number of factors contributing to the length of log phase, which include seeding density."

- The Examiner admits that "seeding density is established in the art as a crucial component of log phase and Huyghe has not provided any information regarding the initial density of cells[.]"

Accordingly, Examiner dismisses the Appellant's conclusions drawn from the Mediatech reference and Mr. Gallagher as "speculative and unsubstantiated." However, since the Examiner contends that a determination of log phase cannot be determined by percentage of confluency, and that Huyghe is silent as to seeding density even though such knowledge is crucial in determining log phase, the Examiner's assertion that the cells of Huyghe are in mid-log at the time of infection is likewise "speculative and unsubstantiated." Therefore it can only be concluded that the Examiner has failed to make a *prima facie* case of anticipation, as per *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) (stating that anticipation "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.")

6. The Dependent Claims – Claims 3, 8, 9, 13, 31 and 58

A. Claim 3 and 58 are Not Anticipated

The Examiner has failed to make a *prima facie* case of anticipation of claims 3 and 58. The Examiner has not shown where Huyghe expressly discloses that the producer cells are essentially homogenous with respect to phase of cell growth. Moreover, the Examiner has not shown that this limitation is inherent. The Examiner simply argues that the 50-60% confluent cells of Huyghe are homogeneous with respect to cell growth. However, as stated in the previous section, the Examiner has admitted that "a definite identification of which log phase a cell culture is in based on a percentage of confluency cannot be determined." If the Examiner contends that phase of cell growth based on confluency, is indeterminable, then it follows that homogeneity of the phase of cell growth based on confluency is likewise indeterminable.

B. Claim 8 is Not Anticipated

The Examiner has failed to make a *prima facie* case of anticipation of claim 8. The Examiner has not shown where Huyghe expressly teaches that producer cells are seeded into the culture medium and allowed to attach to a culture surface for *between* about 3 hours and about 24 hours prior to infection with adenovirus. (Emphasis added). Moreover, the Examiner has not shown that this limitation is inherently disclosed by Huyghe. Instead, the Examiner argues that the claim does not require that the "period of attachment ends at hour 24 or that infection occurs at hour 24." In making this argument, the Examiner ignores the plain language of the claim.

C. Claim 9 is Not Anticipated

The Examiner has failed to make a *prima facie* case of anticipation of claim 9. Claim 9 is the process of claim 1, wherein the culture medium is at least partially recirculated during the adenovirus infection step. The Examiner argues that mixing adenovirus with fresh medium and subsequently introducing this medium to cultured cells during the infection step, as taught by Huyghe, is the equivalent of recirculation. The Appellants contend that Huyghe provides no indication as to whether the culture medium was recirculated. The Examiner mistakes mixing adenovirus and *fresh* media *prior* to cell infection with recirculating the *culture* media *during* infection.

D. Claims 13 and 31 are Not Anticipated

The Examiner has failed to establish a *prima facie* case of anticipation of claims 13 and 31. The Examiner has not shown where Huyghe teaches, either expressly or inherently, the placement of adenovirus in a pharmaceutically acceptable composition after purification.

Huyghe appears silent as to whether any composition containing adenovirus is "pharmaceutically acceptable". Moreover, the Examiner has not provided any basis in fact or technical reasoning, as per *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) contravening the Appellants' position.

7. Claims are Not Obvious

A. Claims 10-12 are Not Obvious Under 35 U.S.C. §103(a) Over Huyghe

In order to establish a *prima facie* case of obviousness, it is the Examiner's burden to show that the prior art references (1) teach or suggest all the claim limitations; (2) there must be some suggestion or motivation to modify the reference or to combine reference teachings; (3) there must be a reasonable expectation of success. See *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed Cir. 1991). As discussed in the appeal brief, there is no *prima facie* case of obviousness of claims 10-12 over Huyghe as not one of the three independent requirements is met. First, Huyghe provides no motivation or suggestion to a person of ordinary skill that one should determine seeding density in order to infect producer cells with adenovirus between mid-log and stationary phase of growth. Second, Huyghe provides no reasonable expectation of success to practice the claimed invention, because, as the Examiner has stated, "seeding density is established in the art as a crucial component of log phase and Huyghe has not provided any information regarding the initial density of cells[.]" Third, Huyghe does not appear to teach or suggest all the claim limitations. More specifically, instead of teaching the claim limitations of claims 10-12 (infection between mid-log to stationary phase of growth as determined by seeding density), Huyghe teaches infection of producer cells based on percentage of confluency.

B. Claim 29 is Not Obvious Under 35 U.S.C. §103(a) Over Huyghe

The Examiner has not met the burden establishing a *prima facie* case of obviousness of claim 29 over Huyghe. The Appellants point out that the Examiner has not explained how Huyghe teaches or suggests adenovirus preparations meeting the specific purity limitations of claim 29. Instead, the Examiner argues that it would be obvious to "test any one of the properties listed to ensure a good yield of adenovirus." However, claim 29 is not directed to testing adenovirus preparations in hope of a certain purity, but to adenovirus preparations that actually meet a certain level of purity. Huyghe does not teach or suggest adenoviral preparations that meet these limitations.

C. Claims 2 and 50 Are Not Obvious Under 35 U.S.C. 103(a) Over Huyghe and Further in View of Graham (C31) and Leu

The Examiner has failed to meet the burden of establishing a case of prima facie obviousness of claims 2 and 50 over Huyghe and further in view of Graham (C31) and Leu. As discussed in the Appeal Brief and in greater detail below, not one of the three requirements to establish obviousness is met.

1. There is No Suggestion or Motivation to Combine

There is no suggestion or motivation to combine Leu and Graham with the teachings of Huyghe. Several factors lead away from such a suggestion or motivation.

First, Leu, while replete with references to hepatitis A virus, appears devoid of any mention of adenoviruses. Leu mentions viruses which are structurally and biologically distinct from adenoviruses. The Examiner attempts to counter this arugement in answering the Appeal Brief. In particular, the Examiner draws attention to the fact that herpesviruses, which are

disclosed in Leu, and adenoviruses, which are not, both possess a double stranded DNA genome. The Examiner cites Fields Virology for support. However, in reviewing Fields Virology, it appears that the differences between adenoviruses and herpesvirusses outnumber any similarities alleged by the examiner. A brief examination reveals varicella, a type of herpesvirus disclosed in Leu, to be an enveloped virus with a genome of 125 kb in length, and containing at least 70 genes. *In* D.M. Knipe *et al.* (ed.), Fields Virology, 4th ed. Philadelphia: Lippencott Williams & Wilkins; 2001: pages 2709-2710. In contrast, adenoviruses are non-enveloped viruses with a modest genomic size between 30-42 kb in length and containing approximately 15 genes, depending on serotype. *Id.*, at pages 2266-2269.

Second, there is teaching or suggestion from Huyghe that there is a problem in need of being solved. Neither Leu or Huyghe recognize a problem and thus there is no reason why a skilled artisan would turn to this particular aspect of virus production described in Leu. A "patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified." *In re Sponnoble*,160 U.S.P.Q. 237, 243 (C.C.P.A. 1969).

Third, the Examiner's reliance on Graham (C31) is inappropriate. Graham used by the Examiner to argue that cells can be infected at 80-90% confluency, which demonstrates that the teachings of Leu are applicable to adenovirus infection at late-log phase of growth. However, as stated previously, there is no motivation to combine the teachings of Huyghe with the teachings of Leu and Graham. The only motivation that the Examiner provides for turning to the Leu reference for its timing of infection is that Leu lists several virus families for which its cell culturing techniques could be used. None of which are adenoviruses. "[I]t is impermissible within the framework of 35 U.S.C. § 103 to pick and choose from any one reference only so

much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art." *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 230 U.S.P.Q. 416 (Fed. Cir. 1986).

2. There is No Reasonable Expectation of Success

There is no reasonable expectation of success in growing the adenovirus of Huyghe with the cell culture method taught by Leu. As discussed in the Appeal Brief, several factors lead away from such a suggestion or motivation to combine. First, it is known in the art that some of the viruses disclosed in Leu, such as herpesviruses and paramyxoviruses possess an envelope with surface projections. Because of this, these viruses require an isotonic osmolarity in order to achieve stability and prevent damage to their envelope membrane. In contrast, adenoviral stability may be achieved at relatively hypertonic osmolarity as adenoviruses lack an envelope. Second, the replication cycle of these two viruses disclosed in Leu are distinct from adenoviruses and involve proteins of their respective envelopes. Third, following entry into the host cell, these viruses require specific enzymes for transcription, such as thymadine kinase for herpes viruses and RNA dependent RNA polymerase for paramyxoviruses. Accordingly, methods involving such different viruses, with different replication strategies provides no reasonable expectation of success in growing the adenovirus of Huyghe with the cell culture methods applicable to the viruses disclosed by Leu. Merely believing that Leu is applicable to the general viral propagation art does not make it so, and does not make its teachings relevant to adenoviruses.

3. The Combination of the References Does Not Teach or Suggest All the Claim Limitations

Finally, Huyghe, when combined with Leu and Graham, does not teach or suggest all the claim limitations. The Appeal brief lists reasons why such a combination cannot exist.

First, the Examiner has not pointed out, and the Appellants cannot find, any mention of 293 cells taught by Huyghe, within the Leu reference. Instead, the Examiner, in answering the Appeal Brief, argues that MRC-5 cells may be used in the propagation of adenoviruses as evidenced by Sheer (U.S. Patent 5,106,841). In making this connection, the Examiner disregards the particular adenovirus of Huyghe, namely, an adenoviral vector with a deletion in the E1 region of the genome that must be complemented in *trans* with an E1 expressing cell line. The Examiner has not shown that MRC-5 cells express E1, nor are the Appellants aware of MRC-5 cells possessing such a property. Accordingly it appears to the Appellants that the E1 deleted adenoviral vector of Huyghe is not combinable with the virus production methods of Leu.

Second, the Examiner has failed to adequately explain how Leu can be combined with Huyghe to teach any benefit of the particular timing of infection as cited in the claims. The Examiner has not shown that Leu teaches that this timing leads, for example, to increased hepatitis A production.of using the particular timing of infecting the cell culture at the time that is recited in the claims- that is, late log or early stationary phase of growth.

D. Claims 26-28 are Not Obvious Under 35 U.S.C. 103(a) Over Huyghe and Further in View of Graham (C7).

The Examiner has failed to meet the burden of establishing a prima facie case of obviousness of claims 26-28 over Huyghe and further in view of Graham (C7). The combination of Huyghe and Graham does not teach or suggest all the claim limitations. Specifically, Claims 26-28 depend from claim 1. Huyghe does not teach or suggest all the elements of claim 1. Graham is cited only for its teaching of 5% deoxycholate. Accordingly the addition of Graham does not cure the deficiencies of Huyghe. Moreover, the citation of deoxycholate does not provide any motivation to combine the references.

E. Claims 4, 30, 39-46 and 48 are Not Rendered Obvious Under 35 U.S.C. §103(a) Over Huyghe and Further in Above and Further in View of Garnier and Spier

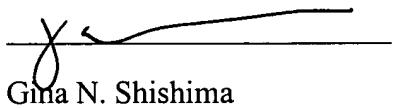
The Examiner has not met the burden of establishing a prima facie case of obviousness of claims 4, 30, 39-46 and 48. First, Huyghe, Garnier and Spier, either alone or in combination do not teach or suggest all the claim limitations. More specifically, the Examiner has not shown where any of these references teach infection at mid-log phase. In the Examiner's Answer, it is argued that Kuchler is evidence of mid-log phase of infection. However, as stated supra, the reliance on Kuchler is both inappropriate and indicates the time of infection as taught by Huyghe to be before mid-log. Second, there is no motivation to combine the references of Huyghe with Garnier and Spier. Garnier concerns only the increased production of heterologous proteins using an adenovirus expression system and does not concern the production of adenovirus. In responding to the Appellant's Brief, the Examiner has argued that Garnier states that one of the goals of the method is to increase adenovirus stocks. However, it appears to the Appellants, that the reference makes it clear that the goal is heterologous protein production using adenoviral vector expression systems rather than the production of adenoviral stocks. The Federal Circuit has held in *In re Mills*, 916 F.2d 680, 682 (Fed. Cir. 1990), that the mere fact that combination or modification of a reference or references is possible does not establish obviousness of the resultant combination unless the prior art also suggests the desirability of the combination, *i.e.*, unless the prior art provides motivation to produce the resultant combination. As stated in the Appellant's Brief, it would seem that the reference teaches conditions to increase production of the heterologous proteins at the expense of virus production, thereby teaching away from the claimed invention. Furthermore, in Spier, which appears to offer a review of various cell culture

methods, the Examiner has not shown, nor can the appellants find, any mention of adenoviruses or any suggestion of a culture method that would support their propagation.

CONCLUSION

In light of the foregoing comments, Appellants submit that the appealed claims meet the requirements for patentability. Therefore, Appellants respectfully request that the Board reverse each of the rejections.

Respectfully submitted,



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